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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,682	02/02/2005	Paul G Shiels	0380-P03437US0	4505

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EXAMINER	
MONTANARI, DAVID A	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,682	SHIELS, PAUL G	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *5,6,11-17,20-27 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 7-10, 18-19, 28-29, and 31-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Non-Final Office action mailed 7/25/2006 is withdrawn.

2. A new examiner has taken over prosecution of the instant application.

3. It is noted that Group VI was erroneously examined in response to the Restriction Requirement mailed 1/27/2006. Applicant had elected Group I (with further election of telomere binding protein G22P1, thus both Groups I and VI will be examined in the instant office action.

4. Claims 1-4, 7-10, 18-19, 28-29, and 31-35 are examined in the instant application.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2), see for example page 18 , which disclose numerous sequences without assigned numbers. Sequences appearing in the specification must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). Specifically, the sequences on page 18 require sequence identifiers. This application clearly fails to comply with requirements of 37 C.F.R 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published in the *Federal Register* at 65 FR 54604 (September 8, 2000) and 1238 OG 145 (September 19, 2000). Applicant must provide an

initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy or compact disc copy of the "Sequence Listing", as well as an amendment directing its entry into application. Applicant must also provide a statement that the content of the sequence listing information recorded in computer readable format is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 C.F.R. 1.821 (e), 1.821 (f), 1.821 (g), 1.825 (b), 1.825 (d).

For the response to this office action to be complete the applicant is required to comply with the Requirements for Patent Applications Containing Nucleotide Sequence and/or amino acid sequence disclosures.

Claim Objections

Claims 18,19, 33 and 35 are objected to because of the following informalities: The claims depend from withdrawn claim 15. For the purposes of compact prosecution the limitations of withdrawn claim 15, consistent with the subject matter under examination, will be read into the claims under consideration. However, it is noted that claim 15 has been withdrawn from examination. Appropriate correction is required.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Examples of embedded hyperlinks are present on page3, lines 28-35 and page 5, line 9.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7-10, 28-29, and 31-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-4, 7-10, 28-29, and 31-32 are drawn to a method of screening mammalian donor tissues for predisposition to rejection by comparing telomere-binding proteins levels in the donor tissue to a reference level of expression.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory

facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompass comparing the level of expression of a telomere-binding protein in a donor tissue with an unknown reference level of expression of a telomere-binding protein.

Whereas the nature of the invention is a method of comparing the levels of a telomere-binding protein in a donor tissue to some "standard" reference level of a same telomere-binding protein, the art teaches that such a method would be unpredictable. The art teaches that telomeres shortening occurs with age, and that this has been profiled particularly in kidneys (2000, J. Am. Soc. Nephrol. Vol. 11, pgs. 444-453). Melk et al. teaches that phenomenon of renal aging has a distinct link with the shortening of telomere length and replicative senescence in renal cells (pg. 445, col. 1 parag. 2 last sentence). Melk continues to teach that telomere length varies among the age of the individual that the kidney sample was obtained from (pg. 447, Fig. 1 and Fig. 2). The art continues to teach that among transplanted kidneys there is a shortening of telomeres which is demonstrated in the F344 to LEW rat model of chronic renal transplantation rejection (2003, Am. J. Path., Vol. 162, pgs. 1305-1312). Joosten et al. teach that left kidney of the recipient rat was removed and replaced with a donor kidney, and that seven days later the native right kidney was removed 7 days after transplantation (pg. 1306, col. 1 parag. 3). Joosten continues to teach that transplants were both syngeneic and from LEW to F344 (and vice versa) (pg. 1306, col. 2 parag. 1). Joosten continues to teach that telomere shortening occurs in both F344 and LEW

allografts from day 7 post-transplantation and that transient expression of the cell cycle markers p21 and p16 (known cell cycle regulatory proteins that have been described to be the consequence of telomere shortening) occurs (pg. 1307, col. 2 bridge pg. 1308 col. 1).

The working examples provided by the instant specification teach the F344 to LEW rat model of chronic renal transplantation rejection, and the levels of the cell cycle inhibitors p21 and p16 that correspond to an increase in cell senescence or shortening of telomeres (pg. 65-69). The specification continues to teach that telomere length was compared with control kidneys that were not transplanted and that p21 and p16 (cell cycle markers) protein levels were compared among transplanted kidneys and normal FEW kidneys (pg. 69 lines 6-28). However the specification fails to teach how the skilled artisan would screen mammalian donor tissues using the claimed method. At first issue is, the reference level of telomere-binding protein expression that is being compared to from the donor tissue. The specification fails to teach and there appears to be no art available anywhere, that teaches any reference level of telomere-binding that correlates to tissue rejection or a predisposition of rejection. If the artisan were to measure TBP in a kidney, they would need to look for TBP levels which indicate rejection or acceptance. Where would they look? Not to the specification and not to the art. No, the skilled artisan would need to invent the reference levels of TBD in order to carry out the claimed invention. The reference levels of TBP are critical to the invention. Their lack of availability renders the claimed invention not enabled. More problematic is, how the reference level comparison should be carried out. Should it be among two kidneys of exact age? Both disease free? The specification gives no guidance on what exactly should be a reference level of a telomere-binding protein. Is the reference level of a telomere-binding protein affected by age, smoking, disease, genetics,

etc.? All of these questions would need to be answered by the skilled artisan before a reference level could be compared to, to enable the method as claimed. While the art discloses and association between telomere shortening and the relationship to cellular senescence, no such association with telomere-binding proteins to a particular tissue rejection has been made. Thus the skilled artisan would require and undo amount of experimentation without a predictable degree of success to make and use the method claimed.

Claims 7, 18, 19, 33 and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of treatment of donor tissues to reduce the risk of rejection comprising treating the tissue with an agent to modulate the activity, half-life or expression and optionally, the effective functionality of at least the G22P1 telomerase binding protein or any homologues or analogues thereof, further comprising treating the tissue with an agent to prevent tissue senescence or cell death. The claims encompass a genus of proteins that are defined by the fact that they are homologues or analogues of the G22P1 protein.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. While the specification contemplates modulating the activity, half-life or expression and optionally, the effective functionality of at least the G22P1 telomerase binding protein or any homologues or analogues thereof, it does not provide any defining characteristics of the homologues or analogues of the G22P1 protein

(Specification pg. 4, line 32-pg. 5 line 9).

The factors to be considered when assessing possession of the claimed invention include disclosure of complete or partial structure, physical and/ or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In regards to the genus of homologues or analogues of the G22P1 protein, there is no requirement in the claims or the specification that these homologues or analogues retain any particular structural or functional characteristics of the wild-type G22P1 protein. The specification does not contemplate that the claimed homologues or analogues must have any conserved functional domains or structural features in order to be used in the claimed method.

Accordingly, in the absence of sufficient recitation of a distinguishing identifying characteristic, the specification does not provide adequate written description of the claimed genus of proteins that are defined solely by the fact that they are homologues or analogues of the G22P1 protein.

Further, the claims are drawn to a method of treatment of donor tissues to reduce the risk of rejection comprising treating the tissue with an agent to modulate the activity, half-life or expression and optionally, the effective functionality of at least the G22P1 telomerase binding protein or any homologues or analogues thereof. Wherein the agent to prevent tissue senescence is a calcineurin inhibitor or an analogue thereof. The claims encompass a genus of analogues of any calcineurin inhibitor.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The specification contemplates a genus of analogues of any calcineurin inhibitors, but does not provide any guidance on the characteristics

of said analogues (Specification pg. 5, line 30-pg. 6 line 7).

The factors to be considered when assessing possession of the claimed invention include disclosure of complete or partial structure, physical and/ or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In regards to the genus of analogues of any calcineurin inhibitors, there is no requirement in the claims or the specification that these homologues or analogues retain any particular structural or functional characteristics of any calcineurin inhibitor. The specification does not contemplate that the claimed analogues must have any conserved functional domains or structural features in order to be used in the claimed method.

Accordingly, in the absence of sufficient recitation of a distinguishing identifying characteristic, the specification does not provide adequate written description of the claimed genus of agents defined solely by the fact that they are analogues of a calcineurin inhibitor.

The Revised Interim Guidelines state, "when there is substantial variation with the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Case law concurs, stating, "simply describing large genus of compounds is not sufficient to satisfy written description requirement as to particular species or sub-genus" *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (CA FC 1996). Furthermore, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description'

inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Thus, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for a genus of proteins that are defined solely by the fact that they are homologues or analogues of the G22P1 protein, or a genus of agents defined solely by the fact that they are analogues of any calcineurin inhibitor. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 18,19,33 and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants claims are drawn to a method of treatment of donor tissues to reduce the risk of rejection comprising treating the tissue with any agent to modulate the activity, half-life or expression and optionally, the effective functionality of at least the G22P1 telomerase binding protein, homologues or analogues, further comprising treating the tissue with an agent to prevent tissue senescence or cell death. Wherein the to prevent tissue senescence agent may be a calcineurin or analogue thereof.

The specification states that an increase in expression of G22P1 expression is indicative of a predisposition to rejection (Specification pg. 4, lines 1-7). Therefore, the disclosure suggests that only decreasing the activity, half-life or expression and optionally, the effective functionality

of G22P1 would lead to a reduction in the risk of rejection of any donor tissue. However, Lee et al teaches that treating cells with an agent that decreases the levels of Ku70 (G22P1) induces apoptosis in the cells because of translocation of Bax from the cytosol to the mitochondria {Lee et al. (2005) Carcinogenesis 26:1716-1730;Abstract; pg. 1723, Fig.4}. Increasing the amount of cell death due to apoptosis in a donor tissue is only likely to increase the risk of rejection. Further, the specification does not provide any guidance demonstrating that modulating the activity, half-life or expression and optionally, the effective functionality of G22P1, homologues or analogues thereof has any effect on the risk of tissue rejection. It is noted that the specification does not provide any guidance as to determine what defines a homologue or analogue of G22P1. Therefore the skilled practitioner would be reduced to guessing as to whether a DNA binding protein was a homologue or analogue of G22P1. The specification provides working examples describing the changes in levels of G22P1 in kidney cells and correlating them with the development of chronic allograft nephropathy (CAN) in kidney transplants (pg. 20, Example 1). However the specification does not provide any guidance that modulating the activity, half-life or expression and optionally, the effective functionality of a marker, such as G22P1, has any effect on the development of CAN in kidneys or the risk of rejection for any other donor tissue.

The art of record teaches that the risks associated with CAN mediated rejection of kidney transplants is associated with the appearance of replicative senescence {Ferlicot et al. (2003) Hum Pathol 34:924-928; Abstract}. However, the distinguishing characteristic and driving force behind replicative senescent cells is the decrease in telomere length below the average telomere length of non-senescent cells (pg. 927, col. 1). Neither the art of record nor the specification provides guidance that modulating the activity, half-life or expression and optionally, the

effective functionality of G22P1 has any effect on telomere length. G22P1 is a helicase, without any known ability to act as a telomerase, and thus is without ability to increase the length of the telomeres. Therefore while the specification provides evidence suggesting that changes in levels of G22P1 in kidney cells correlates with the development of CAN in kidney transplants, there is no evidence provided indicating that G22P1 serves any purpose other than as a possible diagnostic marker of replicative senescence. Finally, neither the specification nor the art of record provide any guidance on any agent that can modulate the activity, half-life or expression and optionally, the effective functionality of G22P1 in order to decrease risk of tissue rejection of any donor transplant. Given the complete lack of guidance in the specification, the skilled practitioner would be reduced to guessing as to what agent could be used to modulate G22P1 in order to decrease risk of donor tissue rejection, and that further a route of administration would also be up to the skilled artisan to determine thus increasing the unpredictability of the claimed invention. Therefore, given the complete lack of guidance in the specification and the art of record, the skilled practitioner would be unable to predict how to practice the invention as claimed, without undue and extensive experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 10, 18, 19, 33 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 recites the limitation "substantially". However, the metes and bounds of "substantially" are not defined by the instant specification with regard to the time the reference level of expression is determined in a sample.

Claim 10 recites the limitation "healthy". However, the term "healthy" is an open-ended term with regard to a tissue sample, and again the metes and bounds of the term "healthy" are not known.

For the purposes of compact prosecution the limitations of withdrawn claim 15, consistent with the subject matter under examination, will be read into the claims under consideration. Regarding claims 18,19,33-35, the phrase "and optionally" in withdrawn base claim 15 renders the claims indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-Tr 8-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 1-571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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